Available online on 15.07.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics
Open Access to Pharmaceutical and Medical Research

Open Access Research Article

FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS FOR ZIDOVUDINE AND LAMIVUDINE COMBINATION USING FRUCTOSE AS OSMOGEN

Chinmaya Keshari Sahoo*[1], Surepalli Ram Mohan Rao[2], Muvvala Sudhakar[3]

[1]Ph.D Scholar, Department of Pharmaceutics, University College of Technology, Osmania University, Hyderabad,Telangana-500007, India

[2]Professor, Mekelle Institute of Technology, Mekelle University, Mekelle, Ethiopia

[3]Professor and Principal, Department of pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500014

ABSTRACT

The present study deals with the development and evaluation of controlled porosity osmotic pump (CPOP) tablets of Zidovudine–Lamivudine. Wet granulation method was used for the development of core tablets. Core tablets were incorporated with HPMCE5 LV polymer, different concentrations of fructose as osmogen and additives. The CPOP tablets were coated with cellulose acetate as a wall forming material, polyethylene glycol as flux regulating agent, and sorbitol acts as pore forming material in SPM. The formulated tablets were evaluated for FTIR, DSC, pre-compression parameters, post compression parameters, *in vitro* drug release study and scanning electron microscopy study. The optimized formulation had no significant effect on the p^H and agitation intensity, but depends on the osmotic pressure of dissolution media indicated that mechanism of drug release. SEM images revealed that no pores were found before dissolution and after dissolution had shown the porous nature of the membrane. Short term stability study at 40±2ºC /75±5% RH for the months on the CF4 formulation indicated that there was no significant change weight variation, % friability, drug content and *in vitro* drug release.

Keywords: HPMCE5LV, wet granulation, CPOP, *in vitro* drug release, stability study.

Article Info: Received 14 May, 2017; Review Completed 30 June, 2017; Accepted 01 July, 2017; Available online 15 July, 2017

Cite this article as:

Sahoo CK, Rao SRM, Sudhakar M, Formulation and evaluation of controlled porosity osmotic pump tablets for Zidovudine and Lamivudine combination using fructose as osmogen, Journal of Drug Delivery and Therapeutics. 2017; 7(4):41-50

DOI: http://dx.doi.org/10.22270/jddt.v7i4.1465

***Address for Correspondence**

Chinmaya Keshari Sahoo, Ph.D Scholar, Department of Pharmaceutics, University College of Technology, Osmania University, Hyderabad,Telangana-500007, India. Email: sahoo.chinmaya83@gmail.com

INRODUCTION

Controlled release dosage forms is the part of modified drug release dosage form which covers a wide range of prolonged [1] action which provide continuous release of their active ingredients at predetermined rate and predetermined time. Out of various controlled drug delivery systems osmotic controlled drug delivery system (OCDDS) utilizes principle of osmotic pressure [2] to control the delivery of active ingredients. The drug released from OCDDS is independent of p^H, hydrodynamic condition of the body and agitation intensity.

The present study is to develop controlled porosity osmotic pump tablets. CPOP tablets were developed where the delivery orifices were formed by the incorporation of a leachable component [3] in SPM. The core is coated with cellulose acetate containing in situ micro pore former sorbitol. Once CPOP tablets come in contact with the aqueous environment of biological system the water soluble component dissolves and an osmotic pumping system is created in the core. Hence water diffuses into the core though the micro porous [4] membrane setting up an osmotic gradient and thereby controlling the release of drug.

Globally AIDS is considered a dangerous disease which is caused by infection with human immune deficiency virus. The final stage of AIDS where the CD4+ count declines to 200cells/µL. Out of various treatments now antiretroviral [5] therapies plays a vital role for controlling the progression of AIDS. Combination therapy is used to be the advanced care of HIV infected patients. The current formulation containing 300 mg Zidovudine and 150 mg of Lamivudine has been formulated as an oral therapy (tablet) for the treatment of HIV-1 infection in adults. The development of this fixed dose combination [6] aims to reduce the number of daily tablets, enhance the compliance therapy and thereby minimizing the risk of emergence of resistance.

MATERIALS AND METHODS

Materials

Zidovudine and Lamivudine were obtained from Hetero Drugs Pvt. Ltd. India. Fructose and mannitol were purchased from Qualigens Fine Chemicals, India. Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, HPMC E5 LV, magnesium stearate, talc and polyethylene glycol (PEG) 400, 600, 4000, 6000 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Microcrystaline cellulose (MCC) and starch are purchased from Signet Pharma, Mumbai, India. All other solvents and reagents used were of analytical grade.

Compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

In this method individual samples as well as the mixture [7] of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into disc by applying pressure of 10 kg/cm to form a transparent pellet in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer (Bruker, Germany).

Differential Scanning Calorimetry (DSC)

Physical mixtures of drug and individual excipients in the ratio of 1:1 were taken and examined in DSC (Shimadzu DSC-50, Japan).Individual samples as well as physical mixture of drug and excipients [8] were weighed to about 5mg in DSC pan. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50-300^{0}C. Heating rate of 20^{0}C $min^{-1}$was used and the thermogram obtained was reviewed for evidence of any interactions.

Methods

Preparation of CPOP tablets

Wet granulation technique was used to develop CPOP core tablets. Accurately weighed quantities of ingredients mentioned in Table 1 were sifted though sieve No. 30. Lubricant (magnesium stearate) and glidant (talc) were sifted though sieve No. 80.The ingredients were manually blended homogenously in a mortar by way of geometric dilution except lubricant and glidant. The mixture was moistened with aqueous solution and granulated though sieve No.30 and dried in a hot air oven at 60ºC for sufficient time (3-4 hrs). The dried granules were passed though sieve No.30 and blended with talc and magnesium stearate. The homogenous blend was then compressed into round tablets with standard concave punches using 10 station rotary compression machines (Mini press, Karnavati, India).

Table1: Composition of controlled porosity osmotic pump tablets of zidovudine-lamivudine combination

Ingredients (mg)	CF1	CF2	CF3	CF4
ZD	300	300	300	300
LD	150	150	150	150
MCC	150	120	90	60
Starch	50	50	50	50
HPMC E5LV	60	60	60	60
Fructose	30	60	90	120
Magnesium stearate	5	5	5	5
Talc	5	5	5	5
Total weight(mg)	750	750	750	750

Coating of core tablets

The coating solution was prepared taking required ingredients from table 2 and acetone was added quantity sufficient maintaining proper viscosity of solution. The coatings of tablets were performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). Hot air is supplied to tablet bed by rotating lower speed 5-8 rpm initially. The coating of tablets was carried out with the rotation speed of 10-12 rpm. The spray rate and atomizing air pressure were 4-6 ml/min and 1.75 kg/cm^2 respectively. Inlet and outlet air temperature were 50ºC and 40ºC respectively. Coated tablets were dried at 50ºC for 12 h.

Table 2: Coating composition for controlled porosity osmotic pump tablets

Formulation code	CA (g)	PEG 400 (g)	PEG 600 (g)	PEG 4000 (g)	PEG 6000 (g)	Sorbitol (g)	Acetone (mL)
CF1	6	2	0	0	0	0	300
CF2	6	0	2	0	0	0.6	300
CF3	6	0	0	2	0	1.2	300
CF4	6	0	0	0	2	1.8	300

Evaluation of granules

The prepared granules were evaluated for pre compression parameters such as angle of repose, bulk density, tapped density and compressibility index (Carr's index). Fixed funnel method was used to determine angle of repose. The bulk density and tapped density were determined by bulk density apparatus (Sisco, India).

The Carr's index can be calculated by the following formula.

$$\%\text{Carr's index} = \frac{et-eb}{et} \times 100 \quad (1)$$

Where e_t is the tapped density of granules and e_b is bulk density of granules.

Hausner's ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density [9].

Evaluation of tablets [10]

Thickness

The thickness of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan).The limit of the thickness deviation of each tablet is ±5%.

Measurement of coat thickness

Film was isolated from the tablets after 18hs of dissolution and dried at 40^0C for 1h.Thickness was measured by using electronic digital calipers (Absolute digimatic, Mitutoyo Corp. Japan)

Hardness

The hardness of tablets can be determined by using Monsanto hardness tester (Sisco, India).

Friability test

Friability test of tablets was performed in a Roche friabilator (SISCO, India).Twenty tablets of known weight (W_1) were de-dusted in plastic chamber of friabilator for a fixed time of 25 rpm for 4 minutes and weighed again of weight (W_2).The percentage of friability was calculated using the following equation.

$$\%\text{Friability} = F = \left(1 - \frac{W_2}{W_1}\right) \times 100 \quad (2)$$

Where, W_1 and W_2 are the weight of the tablets before and after the test respectively.

Weight variation test

The weight variation test is performed by weighing 20 tablets individually calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

Uniformity of drug content test

Powder is made after triturating 10 CPOP tablets from each batch with mortar and pestle. The powder weight equivalent to one tablet was dissolved in a 100ml volumetric flask filled with 0.1N HCl using magnetic stirrer for 24 h. Solution was filtered though Whatman filter paper No.1 diluted suitably and analyzed spectro photometrically

Diameter of tablet

The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan).

***In vitro* dissolution studies**

The *in vitro* dissolution [11] studies were carried out using USP apparatus type II (Lab India 8000) at 75 rpm. For the first 2 h the dissolution medium was 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8 from 3-8 h (900 ml), maintained at 37±0.5^{0}C. At each time point 5 ml of sample was withdrawn and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer (UV-1800, Shimadzu, Japan).

***In vitro* drug release kinetic studies [12, 13]**

In order to investigate the mode of release from tablets, the release data of formulation was analyzed zero order kinetics, first order kinetics, Higuchi model and Korsmeyer-Peppas and Hixson-Crowell equations.

Effect of osmogen concentration

Keeping all the parameters for tablet constant different osmogen [14] concentrations were used to prepare tablets. The drug release was compared with the different osmogen concentration of formulated batches by using USP-II dissolution apparatus.

Effect of pore former concentration

SPM for various batches were prepared by taking different concentrations of pore former [15]. The effect of pore former on *in vitro* release profile is compared as well as number of formation of micropores were observed.

Effect of membrane thickness

Tablets with varying coating thicknesses were developed to demonstrate the effect of coating thickness on drug release. The drug release rate was measured using 0.1N HCl and phosphate buffer pH6.8 as a dissolution medium.

Effect of flux regulating agents

To assess the effect of flux regulating agents on drug release, formulations were developed with different flux regulating agents keeping all other parameters of tablet constant. The drug release was compared with the different flux regulating agents of formulated batches by using USP-II dissolution apparatus.

Effect of osmotic pressure

The effect of osmotic pressure [16] was demonstrated by adding different amount of mannitol of an osmotic agent to produce 30 atm, 60 atm and 90 atm respectively in dissolution media 0.1N HCl for 2 h and phosphate buffer pH 6.8 for remaining hours. The drug release rate was carried out in USP type II (Paddle) apparatus at 75 rpm maintained at 37±0.5^{0}C and compared for various dosage forms.

Effect of pH

The effect of pH [17] for developed formulations were observed by performing the release studies of optimized formulation in different media 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer in pH 7.4 USP type II dissolution apparatus at 75 rpm. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of agitation intensity

The effect of agitation [18] intensity were observed by performing the release studies of optimized formulation in USP Type II (Paddle) dissolution apparatus containing 0.1NHCl for first 2 h and phosphate buffer pH 6.8 for remaining hours at different rotational speeds of 50,100 and 150 rpm with maintaining temperature at 37±0.5°C.The samples were withdrawn at predetermined intervals and analyzed by UV spectrophotometer.

Scanning Electron Microscopy (SEM)

Coating membranes of formulation were collected before and after complete dissolution of core contents and examined for their porous morphology [19] as well as mechanism of drug release by scanning electron microscope (Leica, Bensheim, Switzerland). Scans were taken at an excitation voltage in SEM fitted with ion sputtering device.

Accelerated stability studies

The packed tablets in air tight container were placed in stability chambers (Thermo lab Scientific equipment Pvt. Ltd., Mumbai, India) maintained at 40±2^{0}C/75±5% RH conditions for accelerated testing) for 3 months [20]. Tablets were periodically removed and evaluated for physical characteristics, drug content, *in-vitro* drug release etc..

RESULTS ANS DISCUSSION

FTIR studies:

FTIR spectra (Figure 1) of Zidovudine shows the characteristic absorption peaks for the carbonyl group at 1638.76 cm^{-1}, N=N$^+$=N stretching (azido group) at 2114.50 cm^{-1},C-O stretching at 1063.08 cm^{-1} and amine group stretching at 3317.86 cm^{-1}. Figure 2 shows characteristic absorption peaks of Lamivudine for the C-H stretching at 2843.83 cm^{-1}, N-H bending at 1640.32 cm^{-1},C-N stretching at 1010.71 cm^{-1},O-H in plane bending at 1054.55 cm^{-1} and amine group stretching at 3326.6 cm^{-1}.

The major peaks of HPMCE5LV were found at 3880.71, 3810.87, 3713.83, 3669.20, 3601.84, 3566.74, 3557.95, 3473.68, 3222.79, 3117.03, 3066.96, 2982.59, 2887.86, 2847.2, 2803.12, 2710.75, 2618.99, 2444.13, 2335.14,2068.70, 1661.47, 1536.52, 1500.67, 1424.62, 1071.87, 781.05 and 584.97 cm^{-1}.The major peaks of fructose were found at 3450.75, 3120.47, 3047.75, 2722.80, 2464.30, 2310.70, 2102.48, 1914.04, 1502.21, 1391.71, 1102.14, 787.25, 677.36, and 599.13 cm^{-1}.

In the optimized formulation CF4 peak at 3672.66, 1451.54, 1251.27 and782.94 cm^{-1} were due to presence of the polymer HPMCE5LV.In the formulation the peaks present due to fructose were 2986.84, 1230.38 and 688.81 cm^{-1}.Peaks at 3220.52 and 1065.68cm^{-1} were due to presence of the drug Zidovudine in the optimized formulation and peaks at 1650.23 and 3326.98 cm^{-1} were due to presence of the drug Lamivudine. So from the study it can be concluded that the major peaks of drug 3220.52, 1065.68, 1650.23 and 3326.98 cm^{-1} remain stable and no interaction was found between the drug, polymer and osmogen.

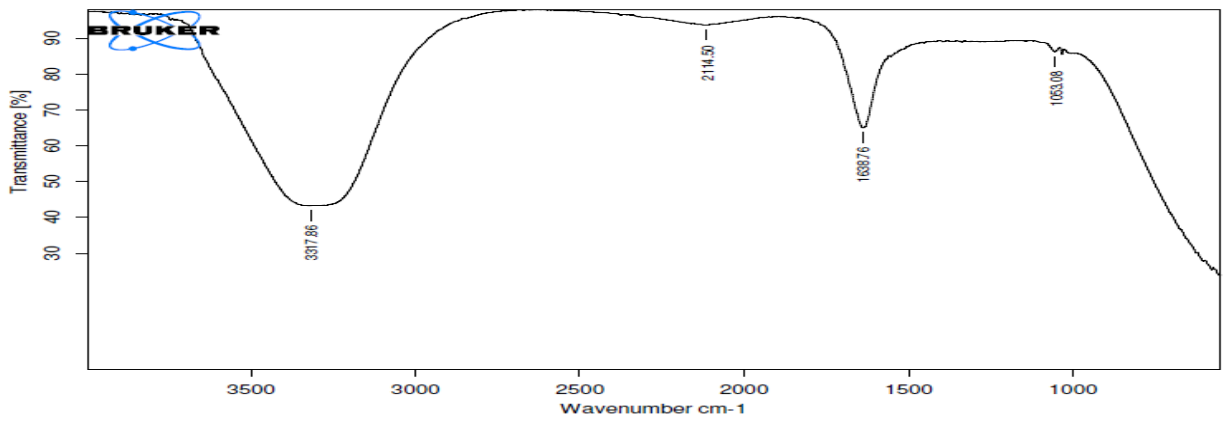


Figure 1: FTIR spectroscopy study of pure Zidovudine

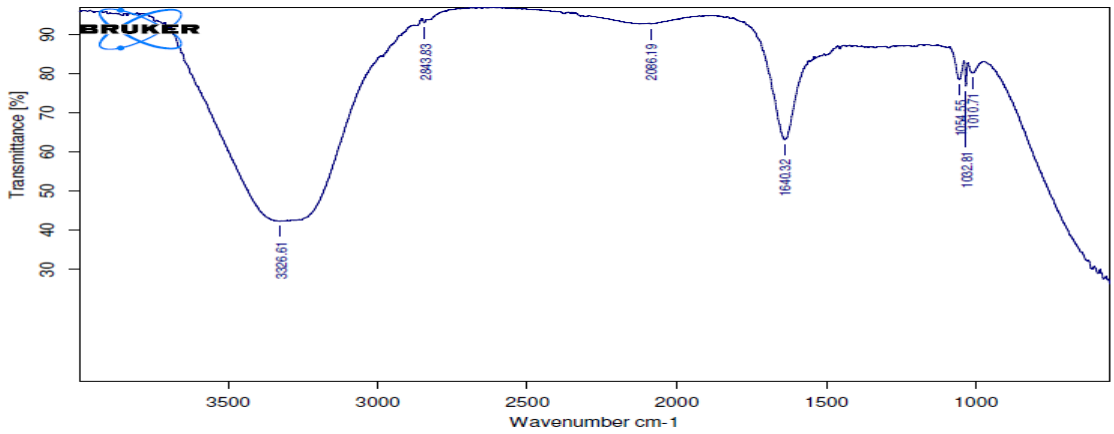


Figure 2: FTIR spectroscopy study of pure Lamivudine

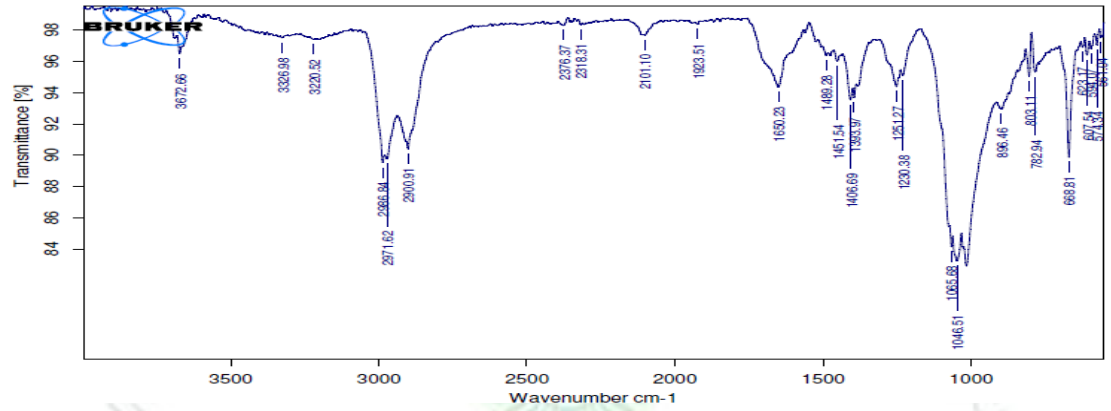


Figure 3: FTIR spectroscopy study of CF4

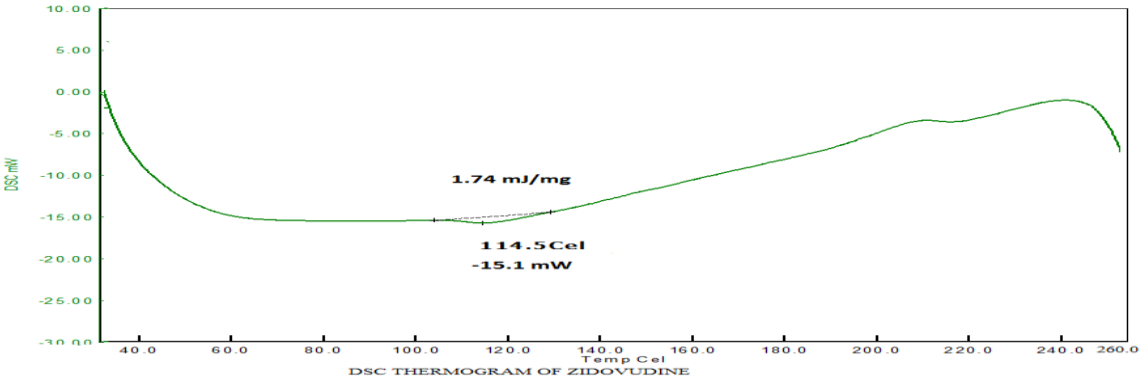


Figure 4: DSC study of Zidovudine

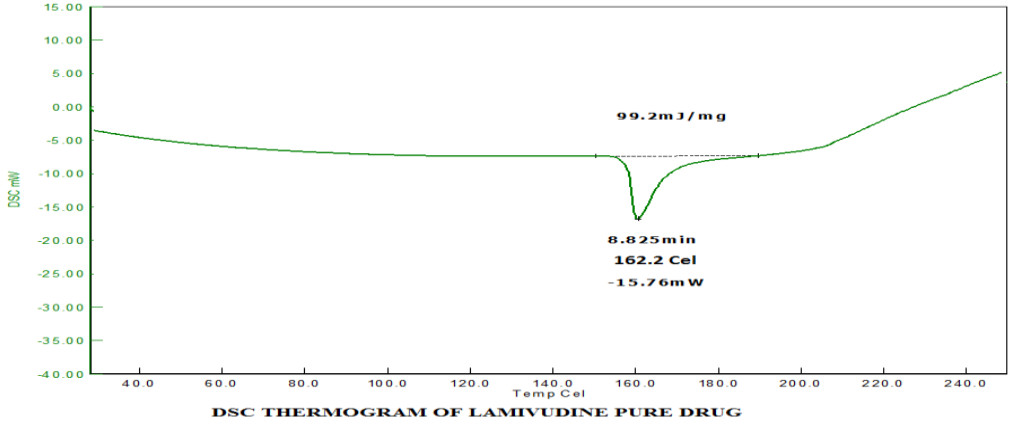


Figure 5: DSC study of Lamivudine

DSC Study

Figure 4 indicates that the endothermic peak of Zidovudine is at 114.5^{0}C.The endothermic peak of Lamivudine is showing at 162.2^0 C (Figure 5).The endothermic peak of CF4 formulation (Figure 6) is showing at117.6^{0}C for Zidovudine and 171.2^{0}C for Lamivudine. There were no significant changes in the endotherm peak between drug and formulation.

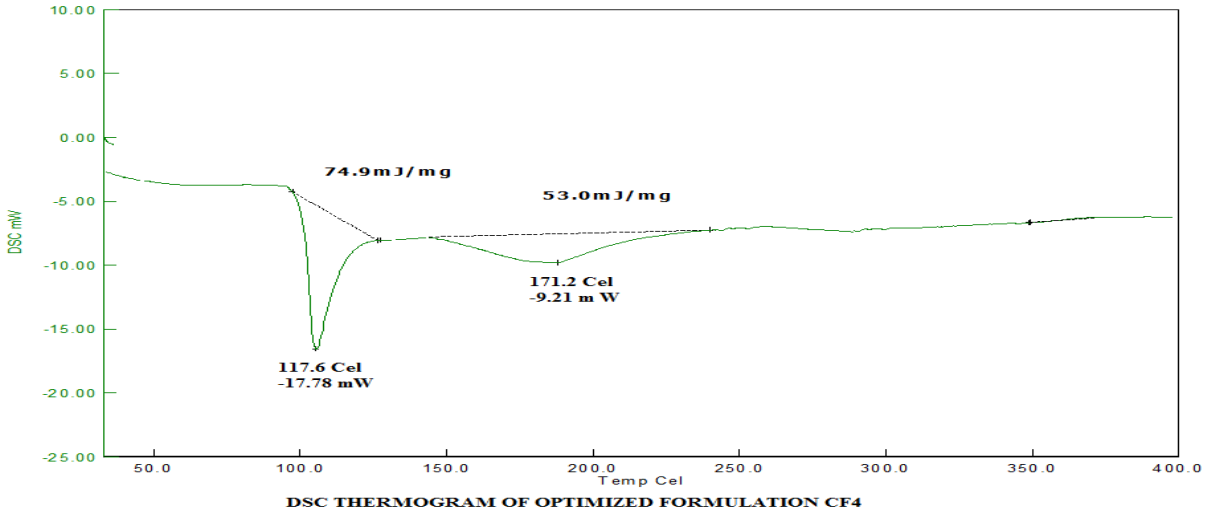


Figure 6: DSC study of CF4

Pre compression parameters:

All the compressible excipients for various batches were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. All the values were within acceptable limits. It is given in Table 3.

Post compression parameters

Tablets were evaluated for different post compression parameters such as thickness, coat thickness, hardness, %friability, drug content and diameter. All evaluated values were in acceptable limits. It is mentioned in Table 4.

Table 3: Pre compression parameters of powder blend

Formulation code	Angle of repose (degree)[a]± S.D	Bulk density (g/ml)[a]± S.D	Tapped density (g/ml)[a]± S.D	Carr's Index (%)[a]± S.D	Hausner's Ratio[a]± S.D
CF1	27.39±0.12	0.494±0.08	0.536±0.14	7.83±0.08	1.08±0.14
CF2	26.20 ±0.13	0.492±0.06	0.538±0.12	8.55±0.06	1.09±0.12
CF3	25.08 ±0.13	0.488±0.12	0.524±0.11	6.87±0.08	1.07±0.11
CF4	24.12 ±0.14	0.485±0.13	0.518±0.12	6.37±0.06	1.06±0.12

All values are expressed as mean± S.D, [a] n = 3

Table 4: Post compression parameters of CPOP tablets

Formulation code	Thickness (mm)[a]± S.D	Coat thickness (µm)[a]± S.D	Hardness (kg/cm^2)[a] ±S.D	%Friability (%)[b] ± S.D	%Weight variation (%)[b]	%Drug content (%)[a] ± S.D(ZD)	%Drug content (%)[a] ± S.D (LM)	Diameter (mm)[a]± S.D
CF1	4.02±0.12	251.3±3.1	6.9±0.12	0.15±0.04	1.59±0.22	99.16±0.83	99.02±0.83	10.11±0.04
CF2	4.05±0.14	200.7±2.9	6.7±0.13	0.17±0.05	1.45±0.21	98.88±0.64	98.05±0.64	10.61±0.06
CF3	4.03±0.12	150.6±3.3	7.3±0.12	0.18±0.06	1.28±0.13	99.44±0.52	99.11±0.52	10.15±0.04
CF4	4.02±0.03	100.6±3.1	6.6±0.11	0.13±0.09	1.12±0.25	100.0±0.59	99.47±0.59	10.03±0.02

N.B.-All values are expressed as mean± S.D, [a] n = 10, [b] n = 20

In vitro dissolution study

The *in vitro drug* release characteristics were studied in 900ml of 0.1N HCl (pH1.2) for a period of first 2 h and 3 to 8 h in phosphate buffer pH 6.8 using USP type II dissolution apparatus (Paddle type). The cumulative percentage drug release of Zidovudine for CF1, CF2, CF3 and CF4 were 82.03±1.98, 84.41±1.83, 89.37±1.21, and 94.14±1.22 respectively at the end of 8 h. It is shown in figure 7. Similarly the cumulative percentage drug release of Lamivudine for CF1, CF2, CF3 and CF4 were 85.86±1.89, 89.96±1.93, 92.34±1.92, and 96.89±1.02 respectively at the end of 8 hrs. It is shown in figure 8.

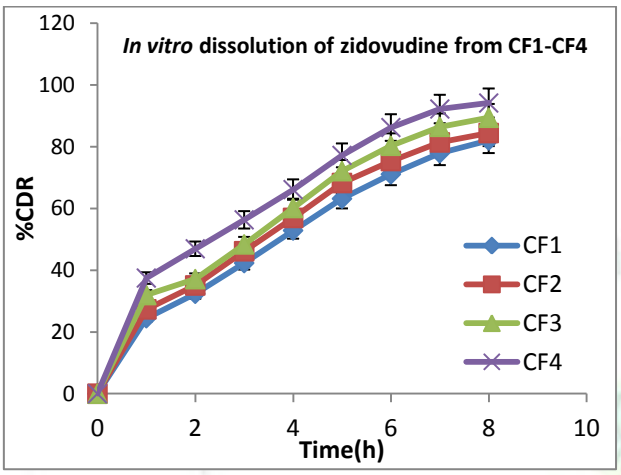


Figure 7: *In vitro* release profiles showing Zidovudine release from various fabricated formulations CF1-CF4 (n=3)

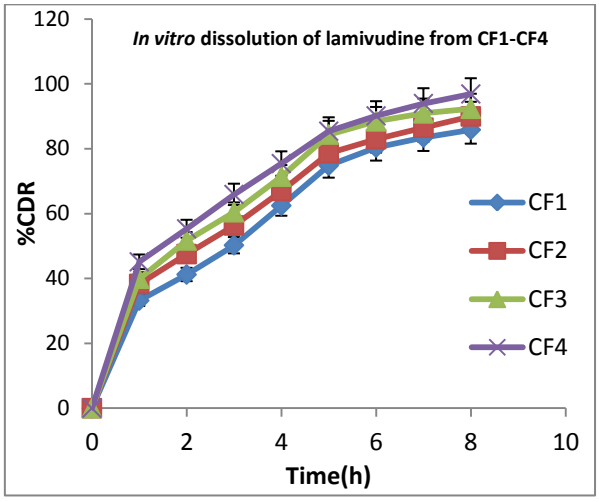


Figure 8: *In vitro* release profiles showing Lamivudine release from various fabricated formulations CF1-CF4 (n=3)

Kinetic model

From the kinetic it is observed that all the formulations follow non-Fickian transport mechanism for Zidovudine as the n value is showing more than 0.45 in all formulations. It is shown in table 5.Similarly for Lamivudine the kinetic study was observed showing CF1 non-Fickian transport mechanism and CF2, CF3 and CF4 follow Fickian diffusion mechanism for Lamivudine. It is shown in table 6.

Table 5: Fitting of IVDR data for Zidovudine from combination in various mathematical models

Models(Z)	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
Batches	R^2	K_0	R_1^2	K_1	R_H^2	K_H	R_K^2	Kkp	n	R^2	Ks
CF1	0.964	9.779	0.991	0.209	0.982	30.09	0.987	22.75	0.618	0.995	0.248
CF2	0.948	10.04	0.992	0.232	0.987	31.22	0.984	25.46	0.585	0.992	0.266
CF3	0.943	10.51	0.982	0.278	0.984	32.75	0.964	28.64	0.549	0.989	0.301
CF4	0.912	10.66	0.972	0.347	0.994	33.94	0.983	35.31	0.475	0.987	0.345

Table 6: Fitting of IVDR data for Lamivudine from combination in various mathematical models

Models(L)	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
Batches	R^2	K_0	R_1^2	K_1	R_H^2	K_H	R_K^2	Kkp	n	R^2	Ks
CF1	0.909	9.953	0.986	0.246	0.989	31.64	0.975	31.18	0.502	0.975	0.275
CF2	0.880	9.958	0.990	0.278	0.991	32.2	0.983	36.64	0.439	0.976	0.295
CF3	0.861	10.33	0.984	0.327	0.986	33.69	0.983	39.17	0.434	0.967	0.330
CF4	0.844	10.38	0.982	0.405	0.985	34.21	0.990	43.85	0.390	0.984	0.371

Effect of osmogen concentration

The concentrations of fructose varied 30, 60, 90, and 120 mg/tab in CF1, CF2, CF3, and CF4 respectively. The cumulative drug release was in order CF4>CF3>CF2>CF1 for both Zidovudine and Lamivudine respectively. It was observed that osmogent enhances the drug release of drug and thus had a direct effect on drug release. The drug release profile was shown in figure 7 for Zidovudine and figure 8 for Lamivudine.

Effect of pore former concentration

Batches CF1 to CF4 the coating composition of pore forming agent of sorbitol were 0%, 10%, 20% ,and 30% w/w of CA of sorbitol respectively. The cumulative drug release was in order CF4>CF3>CF2>CF1 for both zidovudine and lamivudine respectively. It confirms that as the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release.

The drug release profile was shown in figure 7 for Zidovudine and figure 8 for Lamivudine.

Effect of membrane thickness

Release profiles of CPOP tablets from various batches varying the coating thickness were evaluated. The order of coating thickness for CF1 to CF4 is CF1>CF2>CF3>CF4. It was clearly evident that drug release was inversely proportional to coating thickness of the semi permeable membrane. The drug release profile was shown in figure 7 for Zidovudine and figure 8 for Lamivudine.

Effect of flux regulating agents

The concentrations of flux regulating agents (PEG400, PEG600, PEG4000, and PEG6000) were 33.3% w/w of CA in coating solution in CF1, CF2, CF3, and CF4 respectively. The cumulative drug release was in order CF4>CF3>CF2>CF1 for both zidovudine and lamivudine respectively. It is observed that type of flux regulating agents have pronounced effect on drug release. Hence the type of flux regulating agents on drug release is written as PEG6000> PEG4000>PEG600>PEG400. The drug release profile was shown in figure 7 for Zidovudine and figure 8 for Lamivudine.

Effect of osmotic pressure on optimized formulation

The results of release studies of optimized formulation in media of different osmotic pressure indicated that the drug release is highly dependent on the osmotic pressure of the release media. The release was inversely related to the osmotic pressure of release media. This finding confirms that the mechanism of drug release is by osmotic pressure. The drug release of Zidovudine for CF4 was found to be 90.32±1.71% for 30 atm, 86.78±1.72% for 60 atm and 82.43±1.74% for 90 atm respectively. It is shown in figure 9.Similarly the drug release of Lamivudine for CF4 was found to be 93.47±1.74% for 30 atm, 89.16±1.74% for 60 atm and 84.28±1.70% for 90 atm respectively. It is shown in figure 10.

Effect of pH

The optimized formulation CF4 was subjected to *in vitro* drug release studies of Zidovudine and Lamivudine differently in buffers with different pH like pH 1.2, pH 6.8 and pH 7.4. It is observed that there is no significant difference in the release profile for Lamivudine and Zidovudine from combination, demonstrating that the developed formulation shows pH independent release.

Effect of agitation intensity

The optimized formulation of CF4 batch was carried out in USP dissolution apparatus type-II at varying rotational speed (50,100 and 150rpm) for Zidovudine and Lamivudine from combination. It shows that the release of both the drugs from CPOP is independent of agitation intensity.

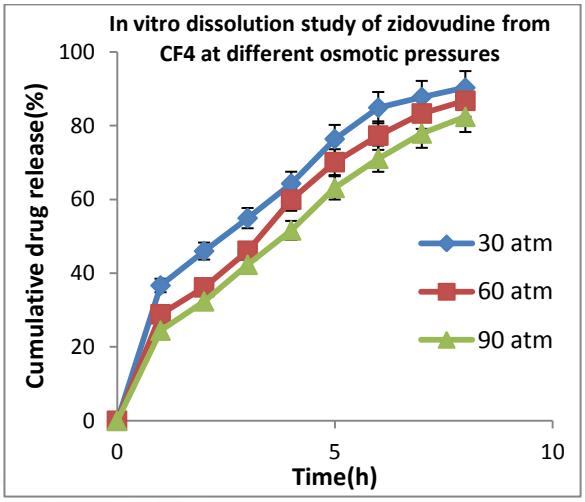


Figure 9: *In vitro* release profiles showing Zidovudine release from best CF4 in different osmotic pressures

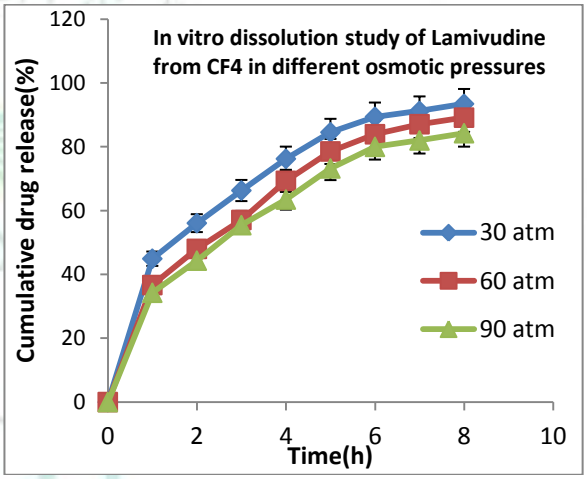
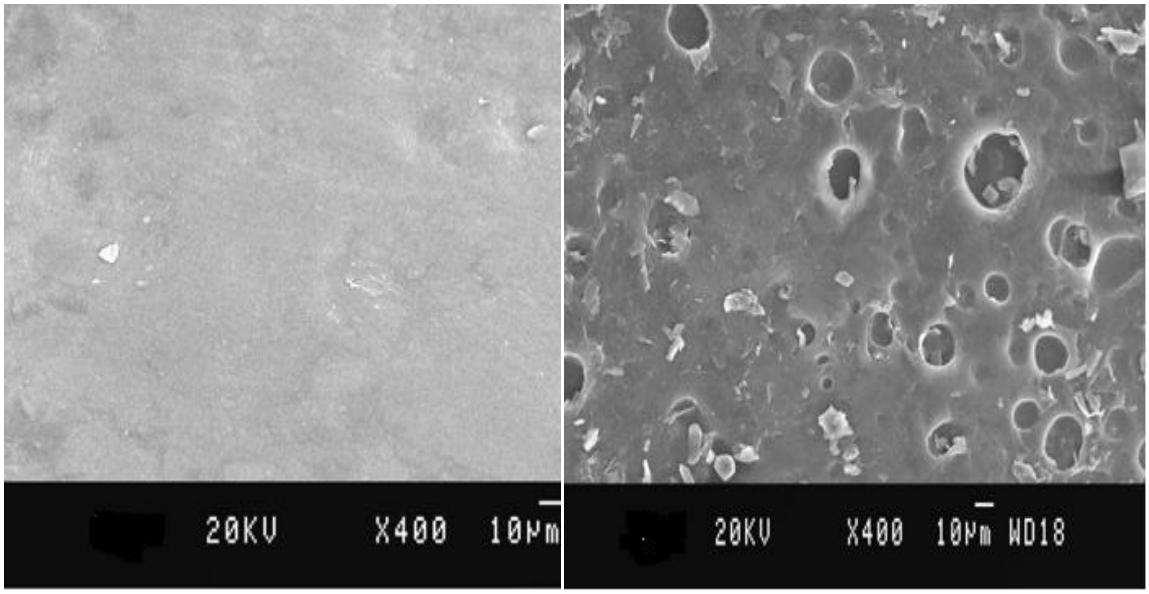


Figure 10: *In vitro* release profiles showing Lamivudine release from best CF4 in different osmotic pressures

Scanning Electron Microscopy (SEM)

The coating membrane of the osmotic delivery system before and after dissolution was examined with the help of SEM. Before dissolution (Figure11a) no pores were found in the coating membrane. But after dissolution (Figure11b) comparatively more numbers of pores were found in the membrane might be due to leaching or removal of entrapped drug from the formulation. The porosity nature of the membrane was due to the presence of pore forming agent sorbitol in the formulation.



a) SEM before dissolution b) SEM after dissolution

Figure 11: a) SEM of membrane structure of optimized formulation before dissolution, b) SEM of membrane structure of optimized formulation after dissolution

Stability studies

From short term stability studies of optimized formulation CF4, it was confirmed that there was no significance changes in physical appearance and drug content. It is shown in table 7.

Table 7: Comparative physicochemical characterization of CF4 at accelerated conditions

S.N.	Parameters	Initial	After 30 days	After 60 days	After 90 days
1.	Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
2.	Thickness(mm)[a] ± S.D	4.02±0.03	4.02±0.03	4.01±0.02	4.01±0.05
3	Hardness(kg/cm^2)[a] ± S.D	6.6±0.11	6.6±0.11	6.5±0.14	6.5±0.12
4.	Friability(%)[a] ± S.D	0.13±0.09	0.13±0.09	0.14±0.08	0.14±0.06
5	Weight variation(mg)[b] ± S.D	1.12±0.25	1.12±0.25	1.13±0.29	1.15±0.25
6.	Drug content(%)[a] ± S.D(ZD)	100.0±0.59	100.0±0.59	99.2±0.52	99.17±0.56
7.	Drug content(%)[a] ± S.D(LM)	99.47±0.59	99.47±0.59	99.11±0.25	99.08±0.32

N.B.-All values are expressed as mean± S.D, [a] n = 10, [b] n = 20

CONCLUSION

The drug release from CPOP was in predetermined rate and predetermined time by incorporating controlled release polymer and osmogen. It was confirmed that increase in concentration of osmogen the drug release from the system was found to be increased.SEM study reveals that the mechanism of drug releases due to osmogen as well as pore former. Hence this can be used to develop newer formulations to avoid shortcomings of conventional dosage forms.

Acknowledgements

The authors would like to acknowledge the contributions of Pharmaceutics Department, Faculty of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India for providing necessary facilities to carry out the research work. This study was part of a PhD thesis under Osmania University, Hyderabad.

REFERENCES

1. Chein YW. Novel Drug Delivery Systems ed by Chein YW, Marcel Dekker, Inc., New York, USA 1992; 139-196.
2. Sahoo CK, Rao SRM, Sudhakar M and Sahoo NK. Advances in osmotic drug delivery system. J of Chemical and Pharmaceutical Research. 2015; 7:252-273.
3. Zenter GM, Rork GS, Himmelstein KJ. The controlled porosity osmotic pump. J control release; 1985; 1:269-282.
4. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J control release; 2000; 79:7-27.
5. Sahoo CK, Sahoo NK, Rao SRM, Sudhakar M. A Review on Prevention and Treatment of Aids. Pharm Pharmacol Int J. 2017; 5(1):00108.
6. Michael J. Mugavero, Charles B. Hicks, HIV resistance and the effectiveness of combination antiretroviral treatment. Drug Discovery Today: Therapeutic strategies 2004; 1(4):529-535.
7. Jilakara VS, Chowdary YA. Formulation and evaluation of sustained release matrix tablets of Zidovudine, Int. J. Pharm. Sci. Rev. Res. 2013; 18(1):143-149.
8. Kumaravelrajan R, Narayanan N, Suba V. Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination. Lipids in Health and Disease.2011; 10:51
9. Sahoo CK, Sahoo NK, Rao SRM, Sudhakar M, Satyanarayana K. A review on controlled porosity osmotic pump tablets and its evaluation. Bulletin of Faculty of Pharmacy, Cairo University, 2015; 53(2):195-205.
10. Sahoo CK, Rao SRM, Sudhakar M. Evaluation of controlled porosity osmotic pump tablets a review. Research J. Pharm. And Tech. 2015; 8(12):119-125.
11. Sirisha VNL, Rao YKK, Eswaraiah MC. Formulation and evaluation of Lamivudine and Zidovudine extended release tablets, Int. J. of Research in Pharmaceutical and Biomedical Sciences.2012;3(4):1759-1763.
12. Costa P, Lobo JMS. Modelling and comparison of dissolution profiles, European J of Pharmaceutical Sciences, 2001; 13:123-133.
13. Sahoo CK, Rao SRM, Sudhakar M and Kokkula S. The kinetic modeling of drug dissolution for drug delivery systems: an overview. Der Pharmacia Lettre 2015; 7(9):186-194.
14. Sharma F, Jain H, Kanzariya V, Upadhyay U. Formulation and evaluation of controlled release osmotic tablet of metoprolol succinate. Asian J. Pharm Clin Res 2014; 7(3):38-43.
15. Banerjee A, Verma PRP, Gore S. Controlled porosity solubility modulated osmotic pump tablets of Gliclazide.AAPS Pharm Sci Tech 2015; 16(3):554-568.
16. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and *in vitro, in vivo* evaluation of extended release matrix tablet of Zidovudine: influence combination of hydrophilic and hydrophobic matrix formers. AAPS Pharm Sci Tech 2006; 7(1):E1-E9.
17. Khan ZA, Tripathi R, Misha B. Design and evaluation of enteric coated microporous osmotic pump tablet (ECMOPT) of quetiapine fumarate for the treatment of psychosis. Acta Poloniae –Drug Research 2012; 69(6):1125-1136.
18. Kanagale P, Lohay BB, Misra A, Davadra P, Kini R. Formulation and Optimization of Porous Osmotic Pump based Controlled Release System of Oxybutynin.AAPS Pharm SciTech. 2007; 8(3):E1-E7. Pore former
19. Rao BP, Geetha M, Purushothama N, Sanki U. Optimization and development of swellable controlled porosity osmotic pump tablet for theophylline. Trop. J. Pharm Res.2009; 8(3):247-255.
20. Cartensen JT. Drug stability: Principle and practices, Marcel Dakker, New York, 2nd ed. 1995; 538-550.